HIGH RISK RHEUMATIC AND MUSCULOSKELETAL AND SKIN DISEASES RESEARCH

RELEASE DATE: October 16, 2003

RFA Number: RFA-AR-04-002

Department of Health and Human Services (DHHS)

PARTICIPATING ORGANIZATIONS:
National Institutes of Health (NIH)
(http://www.nih.gov)

COMPONENTS OF PARTICIPATING ORGANIZATIONS:
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
(http://www.niams.nih.gov/)

CATALOGUE OF FEDERAL DOMESTIC ASSISTANCE NUMBER(S): 93.486

LETTER OF INTENT RECEIPT DATE: November 17, 2003
APPLICATION RECEIPT DATE: December 16, 2003

THIS RFA CONTAINS THE FOLLOWING INFORMATION

PURPOSE OF THIS RFA

The purpose of this initiative is to broaden the base of inquiry in fundamental biomedical, biobehavioral, and biomedical technology research by encouraging applications for research projects that involve an especially high degree of innovation and novelty and, therefore, require a preliminary test of feasibility. The goal is to solicit research applications with the potential for developing groundbreaking technology or methodology that may lead to significant expansion of biomedical research horizons, precipitate a paradigm shift in research, or lead to substantial improvements in human health. Research projects proposed under this Request for Applications (RFA) may involve substantial experimental risks such that their potential for highly significant outcomes may be difficult to judge by the standard criteria used in evaluating investigator initiated (R01) proposals. Preliminary data are not required. The work proposed may not overlap with the aims of currently supported projects or those in which the Principal Investigator has participated during the past five years. Proposed projects must support the mission of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

Two kinds of experienced and established investigators are sought. First, experienced and established investigators in rheumatic or musculoskeletal or skin diseases are encouraged to present a proposal for testing the feasibility of a novel idea, resource or technology. The project should represent a clear and distinctly different approach from the investigator's current and previous (past 5 years) research. Second, experienced and established investigators with no previous work in rheumatic or musculoskeletal or skin diseases are encouraged to apply their expertise to research that is relevant to rheumatic or musculoskeletal or skin diseases. This request for applications should not be considered for new investigators without previous grant experience.

RESEARCH OBJECTIVES

The NIAMS seeks to broaden the base of inquiry in fundamental biomedical, biobehavioral, and biomedical technology research by encouraging research projects that involve a high degree of innovation and novelty. Because innovative projects may require a preliminary test of feasibility, this initiative will provide short-term support for such preliminary work. Each research plan should include a brief description of how the proposed project represents a high degree of innovation and novelty that complements but does not duplicate the applicant's currently funded research. The projects must support the NIAMS mission as detailed in the NIAMS Web page, which can be found at http://www.nih.gov/niams/about/ep1.htm. In brief, the NIAMS supports research in: a) rheumatic diseases; b) cartilage biology and diseases; c) bone biology and diseases (e.g., osteogenesis imperfecta, Paget's disease); d) skin biology and skin diseases; e) autoimmune diseases (e.g., lupus, rheumatoid arthritis); f) connective tissue diseases; g) musculoskeletal diseases (e.g., osteoarthritis, osteoporosis) h) musculoskeletal imaging; i) injuries and disorders of the musculoskeletal system; j) muscle biology and diseases (e.g.,

muscular dystrophy); k) exercise physiology and musculoskeletal fitness; l) sports injuries; m) occupational diseases and injuries; and n) orthopaedic and bioengineering topics.

MECHANISM (S) OF SUPPORT

This RFA will use the National Institutes of Health (NIH) exploratory/developmental research grant, R21, award mechanism. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. Applicants may request up to $50,000 (direct costs) per year for up to two years. These awards are not renewable. If desired, the specific aims of the R21 project may be expanded and serve as the basis for a larger research grant application (R01) submitted prior to the termination of the R21 award. This RFA is a one-time solicitation. This RFA uses just-in-time concepts. It also uses the modular budgeting format. (see http://grants.nih.gov/grants/funding/modular/modular.htm). Specifically, when an application is submitted with direct costs in each year of $250,000 or less, the modular budget format should be used.

FUNDS AVAILABLE

It is anticipated that for FY 2004, approximately $1,200,000 total costs will be available for the first year of support for this initiative. Award of grants is contingent upon the receipt of such funds for this purpose. It is anticipated that up to 20 new grants will be awarded under this program. The specific number to be funded will depend on the merit and scope of the applications received and on the availability of funds. Direct costs are limited to $50,000 and will be awarded in modules of $25,000, less any overlap or other necessary administrative adjustments. Facilities and Administrative costs will be awarded based on the negotiated rates. Applicants may request up to two years of support.

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution has any of the following characteristics:

o For profit or nonprofit organizations
o Public or private institutions, such as universities, colleges, hospitals, and laboratories
o Units of State and local governments
o Eligible agencies of the Federal government
o Domestic or foreign institutions/organizations
o Faith-based or community-based organizations

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

For this solicitation, individuals with an established research career and the skills, knowledge, and resources necessary to carry out the proposed research are invited to work with their institutions to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are strongly encouraged to apply for support from NIAMS programs.

SPECIAL REQUIREMENTS

The Background and Significance Section of application must include a brief section (one page or less) entitled "Eligibility for High Risk RFA" that states the innovative and high risk aspects of the project that distinguish it from currently funded projects in the PI's and collaborators' laboratories. The following concerns should be specifically addressed:

1) Innovation & Novelty: Does the proposed project represent a high degree of innovation and novelty?
2) Lack of overlap with current work: Does the proposed project have specific overlap with current work from the PI? If the proposed work is complementary to ongoing research, why couldn't it be carried out within the framework of currently funded studies?
2) High risk: Explain how the high gain potential of the project, if successful, offsets the high risk of failure.
4) Justification of eligibility of PI: Provide evidence of PI's established research career.

WHERE TO SEND INQUIRIES

We encourage inquiries concerning this RFA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: programmatic/general, peer review, and financial or grants management issues: Direct inquiries regarding programmatic issues to the most appropriate person listed on the web site (http://www.niams.nih.gov/rtac/prog_staff/director.htm) according to scientific area.

o For general inquiries about this RFA contact:

Alan N.Moshell, M.D.
Skin Diseases Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
One Democracy Plaza
6701 Democracy Blvd., Suite 800 Bethesda, MD 20892_4872
Telephone: (301) 594_5017
FAX: (301) 480_4543
Email: alan_n_moshell@nih.gov

o Direct your questions about peer review issues to:

Aftab A. Ansari, Ph.D.
Health Scientist Administrator
NIH-NIAMS
6701 Democracy Blvd, Suite 800
Bethesda, MD 20892
Phone: 301-594-4952
Fax: 301-402-2406
Email: ansaria@mail.nih.gov

o Direct your questions about financial or grants management matters to:

Melinda Nelson
Grants Management Officer National Institute of Arthritis and Musculoskeletal and Skin Diseases One Democracy Plaza
6701 Democracy Blvd. Suite 800
Bethesda, MD 20892_4872
Telephone: (301) 594_3535
FAX: (301) 480_5450
Email: nelsonm@mail.nih.gov

LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent that includes the following information:

o Descriptive title of the proposed research;
o Name, address, and telephone number of the Principal Investigator;
o Names of other key personnel;
o Other participating institutions
o Number and title of this RFA.

Although a letter of intent is not required, is not binding, does not commit the sender to submit an application, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review. The letter of intent should be sent to:

Aftab A. Ansari, Ph.D.
Health Scientist Administrator
NIH-NIAMS
6701 Democracy Blvd, Suite 800
Bethesda, MD 20892
Phone: 301-594-4952
Fax: 301-402-2406
Email: ansaria@mail.nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a DUN and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number can be obtained by calling (866) 705-5711 or through the web site at http://www.dunandbradstreet.com/. The DUNS number should be entered on line 11 of the face page of the PHS 398 form. The PHS 398 document is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

SUPPLEMENTARY INSTRUCTIONS: The research plan (a-d) is limited to 10 pages.
APPLICATIONS THAT EXCEED THE PAGE LIMIT WILL BE RETURNED WITHOUT REVIEW. A Preliminary Data section is not required. If included in R21 applications, it should not exceed one page. The Background and Significance Section of application must include, at the beginning, a brief section (one page or less) entitled "Eligibility for High Risk RFA" in which the PI specifically addresses the following concerns: 1) Innovation & Novelty: Does the proposed project represent a high degree of innovation and novelty? 2) Lack of overlap with current work: Does the proposed project have specific overlap with current work from the PI? If the proposed work is complementary to ongoing research, why couldn't it be carried out within the framework of currently funded studies? 3) High risk: Explain how the high gain potential of the project, if successful, offsets the high risk of failure. 4) Justification of eligibility of PI: Provide evidence of PI's established research career. An appendix may be included in the application; however, the appendix is not to be used to circumvent the page limit of the research plan.

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS:
Applications requesting up to $250,000 per year in direct costs must be submitted in a modular grant format. The modular grant format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in $25,000 modules. Section C of the research grant application instructions for the PHS 398 (rev. 5/2001) at http://grants.nih.gov/grants/funding/phs398/phs398.html includes step by step guidance for preparing modular grants. Additional information on modular grants is available at http://grants.nih.gov/grants/funding/modular/modular.htm.

USING THE RFA LABEL: The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number (AR_03_009) on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the

face page of the application form and the YES box must be marked. The RFA label is also available at: http://grants.nih.gov/grants/funding/phs398/labels.pdf.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the Checklist, and three signed, photocopies, in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892_7710
Bethesda, MD 20817 (for express/courier service)

At the time of submission, two additional copies of the application and all copies of the appendix material must be sent to:

Aftab A. Ansari, Ph.D.
Health Scientist Administrator
NIH-NIAMS
6701 Democracy Blvd, Suite 800
Bethesda, MD 20892
Phone: 301-594-4952
Fax: 301-402-2406
Email: ansaria@mail.nih.gov

APPLICATION PROCESSING: Applications must be received on or before the application receipt date listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within 8 weeks.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfounded application, originally submitted as an investigator-initiated application, is to be submitted in response to an RFA, it is to be prepared as a NEW application. That is, the application for the RFA must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application.

PEER REVIEW PROCESS

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the NIAMS. Incomplete applications will not be reviewed. In addition, applications will be reviewed by NIAMS for responsiveness to the RFA after receipt of application and prior to review. If the application is not determined to be responsive to the RFA, NIAMS staff will either return the application to the applicant or contact the applicant to clarify questions of suitability.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the NIAMS in accordance with the review criteria stated below. As part of the initial merit review, all applications will:

o Undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed and assigned a priority score
o Receive a written critique
o Receive a second level review by the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council.

REVIEW CRITERIA

The goals of NIH supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. For this initiative, the proposed project must have the potential for developing groundbreaking technology or methodology that may lead to significant expansion of biomedical research horizons, precipitate a paradigm shift in research, or lead to substantial improvements in human health. In the written comments, reviewers will be asked to evaluate the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. The scientific review group will address and consider each of the following criteria in assigning the application's overall score, weighting them as appropriate for each application.

o Significance
o Approach
o Innovation
o Investigator
o Environment

The application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out work that by its nature is not innovative but is essential to move a field forward.

SIGNIFCANCE: Does the proposed study have potential for the development of groundbreaking technology or methodology that may lead to significant xpansion of biomedical research horizons, precipitate a paradigm shift in research, or lead to substantial improvements in human health? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Does the investigator acknowledge potential problem areas and consider alternative tactics?

INNOVATION: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or seek to develop new methodologies or technologies? Does the high gain potential of the project, if successful, offset the high risk of failure?

INVESTIGATOR: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

ENVIRONMENT: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, the following items will be considered in the determination of scientific merit and the priority score:

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations, below).

INCLUSION OF WOMEN, MINORITIES AND CHILDREN IN RESEARCH: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria in the sections on Federal Citations, below).

CARE AND USE OF VERTEBRATE ANIMALS IN RESEARCH: If vertebrate animals are to be used in the project, the five items described under Section f of the PHS 398 research grant application instructions (rev. 5/2001) will be assessed.

ADDITIONAL REVIEW CONSIDERATIONS

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

RECEIPT AND REVIEW SCHEDULE

Letter of Intent Receipt Date: November 17, 2003
Application Receipt Date: December 16, 2003
Peer Review Date: June/July 2004
Council Review: September 2004
Earliest Anticipated Start Date: December 2004

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

o Scientific merit (as determined by peer review)
o Availability of funds
o Programmatic priorities.

REQUIRED FEDERAL CITATIONS

HUMAN SUBJECTS PROTECTION: Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm

DATA AND SAFETY MONITORING PLAN: Data and safety monitoring is required for all types of clinical trials, including physiologic, toxicity, and dose-finding studies (phase I); efficacy studies (phase II); efficacy, effectiveness and comparative trials (phase III). The establishment of data and safety monitoring boards (DSMBs) is required for

multi-site clinical trials involving interventions that entail potential risk to the participants. (NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts, June 12, 1998: http://grants.nih.gov/grants/guide/notice-files/not98-084.html).

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH: It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research - Amended, October, 2001," published in the NIH Guide for Grants and Contracts on October 9, 2001 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html); a complete copy of the updated Guidelines are available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS:
The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at http://grants.nih.gov/grants/funding/children/children.htm

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS: NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for research involving human subjects. You will find this policy announcement in the NIH Guide for Grants and Contracts Announcement, dated June 5, 2000, at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

HUMAN EMBRYONIC STEM CELLS (hESC): Criteria for federal funding of research on hESCs can be found at http://stemcells.nih.gov/index.asp and at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see http://escr.nih.gov). It is the responsibility of the applicant to provide, in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s)to be used in the proposed research. Applications that do not provide this information will be returned without review.

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

STANDARDS FOR PRIVACY OF INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION: The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information", the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is

administered and enforced by the DHHS Office for Civil Rights (OCR). Those who must comply with the Privacy Rule (classified under the Rule as "covered entities") must do so by April 14, 2003 (with the exception of small health plans which have an extra year to comply).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent

with the PHS mission to protect and advance the physical and mental health of the American people.

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Department of Health
and Human Services


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